REMARKS

Claims 1, 6, 8, 9, 11, 12, and 15-22 are pending in the present application.

The rejection of Claims 1, 9, and 14 under 35 U.S.C. §112, first paragraph (written description and enablement), are obviated by amendment.

This ground of rejection appears to have at least the following two parts:

(a) the Examiner alleges that the scope of original claims is too broad with respect to the amino acid sequences embraced therein (i.e., the genus of enzymes allegedly lack structural support and can be from any organism or man-made); and

(b) the Examiner alleges that the scope of substrates in the reaction are too broad.

The following arguments were set forth in the response filed on June 8, 2006, and are reiterated herein. Additional comments in response to the Examiner criticisms in the outstanding Office Action follow.

With respect to (a), indeed, it is the current trend in U.S. patent examination to narrow the permissible scope of homologs when DNA or protein sequences are claimed. This case falls right in line with this trend.

However, Applicants submit that application of this trend without full evaluation of the nature of the invention and the scope of the disclosure is inappropriate. At the outset, Applicants submit that the most important feature of the present invention is based on the finding that enzymatic reaction of the specific carboxy and amine component as defined in the present claim 1 enables significantly efficient production of a tri- or longer peptide (the peptide is referred to hereinbelow as a"tripeptide" for the sake of simplicity) in the following manner:

$H_2N\text{-}CH(R^1)\text{-}COO\text{-}R + H_2N\text{-}CH(R^2)\text{-}CONH\text{-}CH(R^3)\text{-}COOH \rightarrow$

$H_2N\text{-}CH(R^1)\text{-}CONH\text{-}CH(R^2)\text{-}CONH\text{-}CH(R^3)\text{-}COOH + ROH$ (Formula (A))[1]

A variety of enzymatic methods for producing tripeptides using other substrates (and therefore in other manner than the aforementioned Formula (A)) have already been known in the prior art. One group of such prior-art methods utilizes intracellular protein synthesis enzymes such as aminoacyl-t-RNA synthetase (see US 5,968,787). *In vitro* protein synthetic methods were also developed using the enzyme. But both of the above-mentioned methods require their users to use very expensive raw materials as the raw materials for peptide synthesis. As such, these prior art methods are not appropriate for industrial use.

Another group of the prior-art methods is the enzymatic method for specified products like vibriolysin (EP 0 302 442 A2) or aspartyl-phenylalanine methyl ester (US 4,284,721). In these references, the use of organic solvents for the peptide synthesis is disclosed. But the methods are not applicable for the industrial use either owing to the low reaction yields for the peptide protection and the negative effect of the solvents of the enzymatic activity.

In summary, productivity of any of such prior-art enzymatic methods is far inferior to that of conventional chemical methods. Therefore, none of enzymatic peptide synthesis in the prior art was successfully performed on an industrial scale.

Contrary to such methods in the prior art, the present invention is significantly more efficient and therefore enables production of tripeptides on an industrial scale with an enzymatic reaction. As such, this method is drastically changing the industry of the peptide

[1] Formula (A) is an example representing where all amino acid residues are alpha amino acids, wherein the carboxy component is an amino acid ester, and wherein the amine component is an unprotected dipeptide. Although this reaction is a typical one, the present invention is not limited thereto.

production. Thus the selection of the substrate (i.e., the specific carboxy and amine component) itself is a great novel feature of the present invention.

Since the selection of the substrate in the present Claim 1 is such an important feature, this feature alone can well define an epoch-making invention in the industry. Therefore, regardless of the broadness of the definition of the enzyme, the present Claim 1 should be is to be allowed in its current form.

More specifically, the Examiner is reminded of MPEP § 2163.02, which states:

> An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

Applicants refer to page 4, lines 10-15 and page 15, line 15 to page 39, line 1, which provides exhaustive detail as to the nature and identity of suitable enzymes to be used in the present invention, as well as methods of cloning, expressing, and purifying the same. As such, Applicants submit that the specification provides an adequate description to allow the skilled artisan to recognize what has been invented and what is claimed is adequately described in the specification within the meaning of 35 U.S.C. § 112, first paragraph.

MPEP § 2164.01 states:

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

Applicants submit that determining what sequences fall within or without the scope of the presently claimed invention be readily apparent to the skilled artisan. At page 15, line 15 to page 39, line 1, Applicants provide a detailed example of how the skilled artisan may

clone, express, and characterize any sequence variant to assess its standing with respect to the claimed invention.

In fact, MPEP §2164.06 states:

> ... quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'

Applicants submit that, with the present specification in hand, determination of sequences that fall within the scope of the presently claimed invention would require nothing more than routine experimentation to determine sequence homology and protein activity. As such, Applicants submit that the claims are fully enabled within the context of 35 U.S.C. §112, first paragraph.

In regard to criticism (b), the Examiner alleges that specification does not sufficiently describe or enable the use of the claimed invention with any amino component and any carboxy component as originally claimed. Applicants disagree with this allegation, but to expedite examination have amended the claims to limit the scope of the substrates as follows. The carboxy component has now been limited to an amino acid ester (such as an alpha amino acid ester H_2N-CH(-R)-COO-R') or an amino acid amide (such as an alpha amino acid amide $H_2N-CH(-R)-CONH_2$), while the amine component has been limited to an unprotected peptide having two or more amino acid residues, a C-protected peptide having two or more amino acid residues, and a peptide having two or more amino acid residues and having a C-terminal amine in place of an amino acid.

Support for the description and enablement of these specifically defined substrates can be found on page 13, line 15 to page 15, line 13 and the Examples. With respect to the Examples, specific mention is made of Tables 13, 16, and 18 where the utility and enablement of several of compounds within the scope of the currently claimed substrates are demonstrated. Specifically, the Examples of the present specification demonstrate a large variety of tripeptide-producing reactions and dipeptide-producing reactions. This demonstration of such a large variety of reaction sis sufficient to conclude that any amino acid ester or amino acid amide can be used as the carboxy component with the claimed genus of amine components. Even though the dipeptide-producing reaction is not within the scope of the claimed invention, the results demonstrated in the Examples (see Tables 5-10, 12, 13, 15, 16, 17-1, 17-2, 17-3, 17-4, and 18) for dipeptide-producing reactions further support the substrate-specificity as presently claimed.

Moreover, Applicants submit that based on the description provided in the specification, the details and experimental protocols outlined in the Examples, and the results set forth in the Examples, the skilled artisan would be readily be able to appreciate and practice the full scope of the presently claimed invention without undue experimentation. As such, Applicants submit that scope of currently claimed substrates are sufficiently described and enabled within the context of 35 U.S.C. §112, first paragraph.

Despite the foregoing, in the outstanding Office Action, the Examiner alleges that Claim 1 is not directed to a method of production of tripeptides using formula (A) and Claim 1 is thus not directed to a method that has high reaction yield, nor directed to an industrially useful method.

However, in amended Claim 1 herein, the carboxy component is now limited to those without protection of H_2N- group. In addition, as claimed, the amine component is also

limited to those without protection of H_2N- group. Despite such an absence of protection, the present method surprisingly results in efficient reaction of -COOR or -CONHR group of the carboxy component and H_2N- group of the amine component to form the -CONH- bond. The newly introduced limitation "wherein said peptide having three or more amino acid residues contains an amino acid residue derived from said carboxy component at the N-terminus thereof" in Claim 1 intends to clarify this feature. Therefore, the Examiner's previous criticisms with respect to the scope of the carboxy and amine components are now believed to be moot.

Further, Applicants submit that in the industrial production of peptides, omitting the protection and de-protection of amino group is a significant advantage. In addition, such a limited invention is sufficiently commensurate with those disclosed and exemplified in the present specification.

Addressing the enablement of the claimed invention under criticism (a) above, the enzymes disclosed in the present specification are those from a bacteria of genus *Sphingobacterium* and of genus *Empedobacter* (although currently withdrawn from consideration as a result of the Restriction Requirement). Therefore, the specification does provide examples from a plurality of species of completely different genus. In addition, the enzymes separated therefrom have homology as low as 63.5%. Further, the present specification discloses a vast variety of combinations of substrates using each of these enzymes. Considering these facts, the present disclosure supports a sufficiently wide variety of embodiments of the claimed invention and should not be limited to any one specific sequence.

In view of the present amendments, Applicants request withdrawal of this ground of rejection.

The rejection of Claims 11, 13, 20, and 22 under 35 U.S.C. §112, first paragraph (enablement), is obviated by amendment.

The Examiner has also taken the position that the recited stringency in Claims 11 and 13 is not stringent enough. The Examiner alleges that the stringency recited therein would effectively allow for a scope of homology of 80% to 90%.

With respect to the Examiner's criticisms with respect to the scope of homologs defined by percent homology (i.e., allegedly 80% to 90%) and hybridization conditions, Applications submit the following. First, with respect to the *stringent* conditions, Applicants submit that such stringent conditions are sufficient to enable the skilled artisan practice the claimed invention without undue experimentation. Further, it should be noted that the Examiner has failed to provide any reason to doubt the object truth of enablement of claims containing these stringency conditions.

To this end, the Examiner is reminded that MPEP §2164.04 states:

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Accordingly, Applicants submit that the Examiner has failed to make out a proper case with respect to the claimed invention based on stringency conditions.

Nonetheless, to expedite examination of the present application, Claims 11, 13, 20, and 22 have been amended based on page 27, lines 19-22 of the specification to define the stringency conditions as 60°C and 0.1xSSC and 0.1% SDS.

In view of the foregoing amendment, Applicants submit that the claimed invention is in full compliance with the enablement requirement of 35 U.S.C. §112, first paragraph.

Accordingly, withdrawal of this ground of rejection is requested.

The rejections of Claims 6 and 8 under 35 U.S.C. §112, first paragraph (written description and enablement), are obviated by amendment.

Indeed, it is the current trend in U.S. patent examination to narrow the permissible scope of homologs when DNA or protein sequences are claimed. This case falls right in line with this trend as Claims 6 and 8 are rejected based on the possibility of mutating "one or a plurality" of amino acid residues and the allegedly limitless number of candidate sequences falling within the scope of this claim. Nonetheless, Applicants wish to direct the Examiner's attention to a recent decision by the U.S. PTO's Board of Patent Appeals and Interferences (*Ex parte Bandman*, **enclosed herewith**) in which the Board held that claims to amino acid sequences that are at least 95% homologous to the disclosed sequence are adequately described and enabled when the specification describes the nucleotide and amino acid sequences.

As in *Ex parte Bandman*, the present specification provides the amino acid sequence (SEQ ID NO: 12) and the corresponding polynucleotide sequence (SEQ ID NO: 11). Further, Claims 6 and 8 has been amended to limit the scope of permissible mutations to one to ten amino acids of SEQ ID NO: 12. Applicants note that SEQ ID NO: 12 is a 619 amino acid protein (see SEQ ID NO: 12 in the Sequence Listing for Claim 8) and Claim 6 defines a 599 amino acid region of SEQ ID NO: 12 (residues 21 to 619). As such, the scope of defined homology is at least 98.4% and at least 98.3%, respectfully. Clearly if the Board finds that under similar circumstances to the present specification an amino acid sequence having at

least 95% homology is adequately described and enabled, the certainly so too is a homolog that is at least 98.3% homolgous.

Further, with respect to the sufficiency of the disclosure for describing the claimed sequence, the Examiner's attention is directed to Example 14 of the Synopsis of Application of Written Description Guidelines which analyzes a situation where a claim covers a protein that is at least 95% identical to a disclosed sequence and has a specific function. In these guidelines, the Patent Office has concluded that such a claim is adequately described within the meaning of 35 U.S.C. § 112, first paragraph

> There is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least *95%* identity to the reference sequence, SEQ ID NO: 3. The single species disclosed is representative of the genus because all members have at least *95%* structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least *95%* identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.
>
> **Conclusion:** The disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention.

As the specification adequately describes the sequences that differ from SEQ ID NO:12 by the inclusion of one to ten amino acid mutations (i.e., at least 98.3% homologous) and the specification describes how one can test for the recited activity to use as substrates an amine component having two or more amino acid residues and a carboxy component, to form a peptide having one more peptide bond than the amine component. Therefore, the claims as presented herein are deemed to be fully described and enabled.

Withdrawal of this ground of rejection is requested.

The rejection of Claims 1, 6, and 8 under 35 U.S.C. §102(b) as being anticipated by Morihara et al is respectfully traversed.

The Examiner has taken the position that Morihara et al disclose enzymological production of tripeptide Ac-Phe-Gly-Ala from Ac-Phe-O-Et (carboxy component) and Gly-Ala (amine component). It should be noted, however, the H_2N- group of the carboxy component in Morihara et al is protected by the acetyl group.

In contrast, in the invention claimed in Claim 1, the carboxy component is limited to those in which the amino group thereof is *unprotected*. Therefore, the present invention is not anticipated by Morihara et al.

Furthermore, with respect to Claim 6, Applicants submit that Morihara et al fails to disclose the sequence of amino acid residues 21 to 619 of the amino acid sequence described in SEQ ID NO: 12 or the same in which one to ten amino acids have been substituted, deletion, insertion, and/or addition which results in a homology of at least 98.3%.

In view of the foregoing, Applicants request withdrawal of the rejections over Morihara et al. Acknowledgment that this rejection has been withdrawn is requested.

The rejections of: (a) Claims 1, 6, 8, 9, 11, and 13-22; (b) 6, 8, and 15-18; and (c) Claim 11, under 35 U.S.C. §112, second paragraph, are obviated by amendment.

Applicants have amended the claims herein to address the Examiner's specific criticisms. For example, the "redundant" language has been removed and antecedent basis for all claim terms has been provided. As such, this ground of rejection is no longer believed to be tenable.

Withdrawal of this ground of rejection is requested.

The objections to Claims 1 and 8 are obviated in part by amendment and traversed in part.

Claim 1 has been amended as suggested by the Examiner. As such, this criticism is now moot. The Examiner objects to the use of the word "and" at the end of line 3 of Claim 8; however, Applicants note that this term is proper and it, in fact, required to separate the terms of the Markush group in this claim. Therefore, the objected to "and" has been left and this objection should be withdrawn.

Withdrawal of this ground of objection is requested.

Finally, the Examiner indicates that Applicants are not entitled to the date of the priority, because the certified translation has not been filed. Therefore, to perfect their claim to priority, Applicants **submit herewith** a certified English translation of JP 2002-218958. Acknowledgment that this objection has been withdrawn.

Applicants submit that the present application is in condition for allowance. Early notification to this effect is respectfully requested.

Respectfully submitted,

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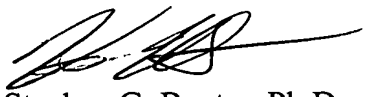

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